

Amendments to the Specification:

Please insert the Sequence Listing being filed concurrently herewith into the specification.

Please amend paragraph 319 on page 90 as follows.

The antisense (AS) strands listed below having SEQ ID NO: 8 were individually duplexed with the sense (S) strand having SEQ ID NO: 7 and the activity was measured to determine the relative positional effect of the 5 modifications.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence</u>
7/271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
8/271071(AS)	3'-dTdT-GUUUAGGUCUCCGAUCGUC-5'
[8] <u>9</u> /271072(AS)	3'-dTdT-GUUUAGGUCUCCGAUCGUC-5'
[8] <u>10</u> /271073(AS)	3'-dTdT-GUUUAGGUCUCCGAUCGUC-5'
[8] <u>11</u> /271074(AS)	3'-dTdT-GUUUAGGUCUCCGAUCGUC-5'
[8] <u>12</u> /271075(AS)	3'-dTdT-GUUUAGGUCUCCGAUCGUC-5'

Please amend paragraph 322 spanning pages 90-91 as shown below.

The antisense strands listed below having SEQ ID NO:9 were individually duplexed with the sense strand having SEQ ID NO:7 and the activity was measured to determine the relative effect of adding either 9 or 14, 2'-O-methyl modified nucleosides at the 3'-end of the resulting siRNA's.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence</u>
7/271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
[9] <u>13</u> /271079(AS)	3'- <u>UUGUUU</u> AGGUCUCCGAUCGUC-5'
[9] <u>14</u> /271081(AS)	3'- <u>UUGUUU</u> AGGUCUCCGAUCGUC-5'

Please amend paragraph 325 spanning pages 91-92 as shown below.

A series of blockmers were prepared as duplexed siRNA's and also as single strand asRNA's. The antisense strands were identical for the siRNA's and the asRNA's. Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence 5'-3'</u>
[10] <u>15</u> /308746 (S)	5'-AAGUAAGGACCAGAGACAAA-3' (PO)
[11] <u>16</u> /303912 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)
[11] <u>17</u> /316449 (AS)	3'- <u>UUCAU</u> UCCUGGUCUCUGUUU-P 5' (PS)
[11] <u>18</u> /335223 (AS)	3'-UUCA <u>U</u> UCCUGGUCUCUGUUU-P 5' (PS)
[11] <u>19</u> /335224 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)
[11] <u>20</u> /335225 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)
[11] <u>21</u> /335226 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)
[11] <u>22</u> /335227 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)
[11] <u>23</u> /335228 (AS)	3'-UUCAU <u>UCCUGGUCUCUGUUU</u> -P 5' (PS)

SEQ ID NO: Sequence (5'-3')

[10] <u>15</u>	AAGUAAGGACCAGAGACAAA
[11] <u>16</u>	UUUGUCUCUGGUCCUACUU

Please amend paragraph 327 on page 92 as follows.

Blunt and overhanging siRNA constructs were prepared having a block of 5, 2'-O-methyl nucleosides at the 3'-terminus.

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence (overhangs)</u>
7/271790 (S)	5'-CAAAUCCAGAGGCUAGCAG-dTdT-3'
[9] <u>24</u> /xxxxxxx (AS)	3'-UUGUUUAGGUCUCCGA <u>UCGUC</u> -5'

<u>SEQ ID NO:/ISIS NO</u>	<u>Sequence (blunt)</u>
[12] <u>25</u> /xxxxxx(S)	5'-GUCAAAUCCAGAGGCUAGCAG-3'
[13] <u>26</u> /xxxxxxx (AS)	3'-CAGUUUAGGUCUCCGAUCGUC-5'

Please amend paragraph 328 spanning pages 92-93 as shown below.

Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

<u>SEQ ID NO:</u>	<u>Sequence (5'-3')</u>
[12] <u>25</u>	GUCAAAUCCAGAGGCUAGCAG
[13] <u>27</u>	CUGCUAGCCUCUGGAUUUGAC

Please amend paragraph 330 on page 93 as follows.

Three siRNA hemimer constructs were prepared and examined in a PTEN assay. The hemimer constructs had 7, 2'-O-methyl nucleosides at the 3'-end. The hemimer was put in the sense strand only, the antisense strand only and in both strands to compare the effects.

<u>SEQ ID NO:/ISIS NO</u>	<u>Constructs (overhangs)</u>
[14] <u>28</u> /271068 (S)	5'-CAAAUCCAGAGGCU <u>AGCAGUU</u> -3'
[9] <u>29</u> / (AS)	3'- <u>UUGUUU</u> AGGUCUCCGAUCGUC-5'
[14] <u>28</u> /271068 (S)	5'-CAAAUCCAGAGGCU <u>AGCAGUU</u> -3'
[9] <u>30</u> / (AS)	3'-UUGUUUAGGUCUCCGAUCGUC-5'
[14] <u>31</u> / (S)	5'-CAAAUCCAGAGGCUAGCAGUU-3'
[9] <u>29</u> / (AS)	3'- <u>UUGUUU</u> AGGUCUCCGAUCGUC-5'

Please amend paragraph 331 on page 93 as follows.

Underlined nucleosides are 2'-O-methyl modified nucleosides, all other nucleosides are ribonucleosides and all internucleoside linkages for the AS strands are phosphorothioate and the internucleoside linkages for the S strand are phosphodiester.

SEQ ID NO: Sequence (5'-3')

[14] 31 CAAAUCCAGAGGCUAGCAGUU

[15] 35

Please amend paragraph 333 on page 94 as follows.

Four hemimers were prepared and assayed as the asRNA's and also as the siRNA's in a PTEN assay. The unmodified sequence was also tested as the asRNA and as the siRNA.

SEQ ID NO:/ISIS NO

Constructs (overhangs)

[10] <u>15</u> /308746 (S)	5'-AAGUAAGGACCAGAGACAAA-3'
[11] <u>16</u> /303912 (AS)	3'-UUCAUCCUGGUCUCUGUUU-P 5'
[11] <u>17</u> /316449 (AS)	3'- <u>UUCA</u> UCCUGGUCUCUGUUU-P 5'
[11] <u>32</u> /319013 (AS)	3'- <u>UUCA</u> UCCUGGUCUCUGUUU-P 5'
[11] <u>33</u> /319014 (AS)	3'- <u>UUCAU</u> CCUGGUCUCUGUUU-P 5'
[11] <u>34</u> /319015 (AS)	3'- <u>UUCAU</u> CCUGGUCUCUGUUU-P 5'

Please amend paragraph 336 spanning pages 94-95 as follows.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-OMe containing monomers. Underlined monomers have PS linkages. Monomers without underlines have PO linkages.

SEQ ID NO/ISIS NO

[15] <u>35</u> /300852	5'-OH-CUG CUA GCC UCU GGA UUU GA	(OMe/PO)
[15] <u>35</u> /300853	5'-P- CUG CUA GCC UCU GGA UUU GA	(OMe/PO)

[15]	<u>36/300854</u>	5'-OH- CUG CUA GCC UCU GGA UUU GA	(OMe/PO)
[15]	<u>37/300855</u>	5'-P- CUG CUA GCC UCU GGA UUU GA	(OMe/PO/PS)
[16]	<u>38/300856</u>	5'-OH- CUA GCC UCU GGA UUU GA	(OMe/PO/PS)
[15]	<u>39/300858</u>	5'-OH- CUG CUA GCC UCU GGA UUU GA	(OMe/PS)
[15]	<u>39/300859</u>	5'-P- CUG CUA GCC UCU GGA UUU GA	(OMe/PS)
[16]	<u>40/300860</u>	5'-OH- CUA GCC UCU GGA UUU GA	(OMe/PS)
[17]	<u>41/303913</u>	5'-OH- GUC UCU GGU CCU UAC UU	(OMe/PS)
[18]	<u>42/303915</u>	5'-OH- UUU UGU CUC UGG UCC UU	(OMe/PS)
[19]	<u>43/303917</u>	5'-OH- CUG GUC CUU ACU UCC CC	(OMe/PS)
[20]	<u>44/308743</u>	5'-P- UUU GUC UCU GGU CCU UAC UU	(OMe/PS)
[21]	<u>45/308744</u>	5'-P- UCU CUG GUC CUU ACU UCC CC	(OMe/PS)
[22]	<u>46/328795</u>	5'-P- UUU GUC UCU GGU CCU UAC UU	(OMe/PS)

Please amend paragraph 337 spanning pages 95-96 as shown below.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-F containing monomers. Underlined monomers have PS linkages. Monomers without underlines have PO linkages. Sense stands (S) are listed 3' -> 5'. Antisense strands (AS) are listed 5' -> 3'.

SEQ ID NO/ISIS NO		Seauence	Features
[23]	<u>47/279471</u>	AS ^m CUG ^m CUA G ^m C ^m C U ^m CU GGA UUU G dTdT (F/PO)	
[24]	<u>48/279467</u>	S ^m CAA AU ^m C ^m CAG AGG ^m CUA G ^m CA G dTdT (F/PO)	
[25]	<u>49/319018</u>	AS UU UGU CUC UGG UCC UUA CUU	(F/PO)
[26]	<u>50/319019</u>	S AAG UAA GGA CCA GAG ACA AA	(F/PO)
[27]	<u>51/319022</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/PS)
[27]	<u>52/333749</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27]	<u>53/333750</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27]	<u>53/333751</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27]	<u>54/333752</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27]	<u>55/333753</u>	AS <u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)

[27] <u>56</u> /333754	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>57</u> /333756	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>58</u> /334253	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>59</u> /334254	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>60</u> /334255	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>61</u> /334256	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>62</u> /334257	AS	<u>UU UGU CUC UGG UCC UUA CUU</u>	(F/OH/PS)
[27] <u>63</u> /317466	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PS
[27] <u>64</u> /317468	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PO
[27] <u>65</u> /317502	AS	<u>UUU GUC UCU GGU CCU UAC UU</u>	PS

Please amend paragraph 339 on page 97 as follows.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Where the antisense strand has a TT 3'-terminus the corresponding sense strand also has a 3'-TT (deoxyT's). Bolded monomers are 2'-F containing monomers. Underlined monomers are 2'-OMe. Monomers that are not bolded or underlined do not contain a sugar surrogate. Linkages are shown in the parenthesis after the sequence.

SEQ ID NO./ ISIS NO.	Composition (5' 3')	Features
[28] <u>66</u> /283546	<u>CUG CUA GCC UCU GGA</u> UUU <u>GU</u> .dT-3'	(OMe/F/PO)
[29] <u>67</u> /336240	UUU GUC UCU GGU CCU UAC <u>UU</u>	(OMe/F/PS)

Please amend paragraph 340 spanning pages 97-98 as shown below.

The following antisense strands of siRNA's were hybridized to the complementary full phosphodiester sense strand. Bolded monomers are 2'-MOE (2'-methoxyethoxy). Linkages are phosphothioate.

SEQ ID NO	Composition	PTEN mRNA level (%UTC) 100 nM oligomer
[30] <u>68</u>	UUC AUU CCU GGU CUC UGU UU	--
[30] <u>69</u>	UUC AUU CCU GGU CUC UGU UU	50
[30] <u>70</u>	UUC AUU CCU GGU CUC UGU UU	--
[30] <u>71</u>	UUC AUU CCU GGU CUC UGU UU	43
[30] <u>72</u>	UUC AUU CCU GGU CUC UGU UU	42
[30] <u>73</u>	UUC AUU CCU GGU CUC UGU UU	47
[30] <u>74</u>	UUC AUU CCU GGU CUC UGU UU	63
[30] <u>75</u>	UUC AUU CCU GGU CUC UGU UU	106